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PHASE 3 SUMMARY OF MRID 00117622 AND RELATED MRIDS 00149529, 00146632, AND 00153876:

6-WEEK INHALATION STUDY IN RATS

STUDY # 483-216

FLUMETRALIN

GUIDELINE REFERENCE:

82-4 90-DAY INHALATION - RAT

SUMMARY PREPARED BY:

JACQUELINE GILLIS, Ph.D.

MERRILL TISDEL

5 OCTOBER 1990

ORIGINAL STUDY PREPARED BY:

HAZLETON LABORATORIES AMERICA, INC.

VIENNA, VIRGINIA

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

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HAZLETON
LABORATORIES AMERICA, INC.

HLA 483-216

COMPLIANCE STATEMENT
Subacute Inhalation Study in Rats
CGA-41065 Treated Cigarettes

This study was conducted in compliance with the Good Laboratory Practice Regulations as set forth in Title 21 of the U.S. Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments. Findings from the inspections and final report review were reported to management and to the study director.

Study Director:

FOR WILLIAM B. COATE, Ph.D.
Life Sciences Division

9/28/80
Date

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR part 160 (see above)

Submitter/Sponsor of Study

Merrill Fisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

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Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP Guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

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82-4 Subchronic Inhalation Toxicity (90-day) in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. Y — Technical form of the active ingredient tested. (for reregistration only)
2. Y — Product is a gas; a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3. Y — At least 10 young adult rats/sex/group
4. N — Dosing, 6 hours per day, 5 days per week for 13 weeks.
5. Y — Food and water should be withheld during dosing.
6.* N — Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
7. N — Chamber temperature, 22° C (±2°), relative humidity 40-60%.
8.* N — Alternatively, oro-nasal or head only exposures may be used.
9. Y — Monitor rate of air flow,
10. Y — Monitor actual concentrations of test material in breathing zone.
11. N — Monitor aerodynamic particle size for aerosols.
12. Y — Individual daily observations.
13. Y — Individual body weights.
14. Y — Individual or cage food consumption.
15.* N — Opthalmoscopic examination (at least pretest and at term) control and high dose.
16. Y — Clinical pathology data of 17 & 18 in all animals at termination.
17. Y — Hematology.
    - Y Erythrocyte count
    - Y Hemoglobin
    - Y Hematocrit
    - Y Leucocyte count
    - * Y Differential count
    - Y Platelet count (or clotting measure)
18. Y — Clinical chemistry.
    - * Y Alkaline phosphatase
    - Y Aspartate aminotransferase
    - Y Alanine aminotransferase
    - * N Creatinine kinase
    - * Y Lactic dehydrogenase
    - Y Glucose
    - Y Bilirubin
    - * Y Cholesterol
    - * N Creatinine
    - Y Total Protein
    - Y Albumin
    - Y Urea nitrogen
    - N Inorganic phosphate
    - Y Calcium
    - * Y Potassium
    - N Sodium
    - * N Chloride
19.* N — Urinalysis, only when indicated by expected or observed activity. As scheduled in 16.
    - ___ Blood
    - ___ Protein
    - ___ Ketone bodies
    - ___ Appearance
    - ___ Glucose
    - ___ Total bilirubin
    - * ___ Urobilirubin
    - ___ Sediment
    - ___ Specific gravity (osmolality)
    - * ___ Volume
20. Y — Individual necropsy of all animals.

Criteria marked with a * are supplemental and may not be required for every study.

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21. Y Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Y aorta	Y jejunum	Y peripheral nerve
Y eyes	Y bone marrow	Y kidneys†
Y caecum	Y liver†	Y esophagus
Y colon	Y lung	Y ovaries
Y duodenum	Y lymph nodes	N oviduct
Y brain†	Y stomach	Y pancreas
Y skin	Y mammary gland	N rectum
Y heart	Y spleen	Y spinal cord (3x)
Y testes†	Y musculature	Y thyroid / parathyroids
Y pituitary	Y epididymis	Y salivary glands
Y ileum	Y adrenals	Y thymus
Y trachea	Y urinary bladder	Y accessory sex organs; uterus
NA gall bladder		

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.

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IDENTIFICATION OF TEST MATERIAL

Chemical Name

CAS Name: N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine

or

2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine

Common Name: Flumetralin

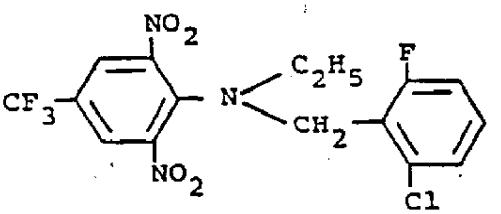
Trade Name: Prime +®

CIBA-GEIGY Code Number: CGA-41065

CAS Registry Number: 62924-70-3

EPA Shaughnessy Number: Unknown

Chemical Structure:



Percent Active Ingredient

92% minimum

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Flumetralin: 82-4: Subchronic Inhalation Toxicity in the Rat

1. The test article was Flumetralin (CGA-41065) Technical, FL-810973, purity 96.4%.

2. The test article is a bright orange crystalline substance. After being micronized, it was used to spike 2R1 filler tobacco at levels of 300, 5000, and 15000 ppm CGA-41065. The tobacco was then made into cigarettes and the test article was administered as pyrolysis residues carried by cigarette smoke. The vehicle control substance was smoke from cigarettes made from 2R1 filler tobacco which had not been spiked with the test article.

3. There were ten male and ten female Fischer 344 albino rats in each of three test groups (300, 5000, and 15000 ppm) and a concurrent vehicle control group (no-residue tobacco). An additional ten male and ten female rats were used for pre-exposure clinical pathology determinations but were not included in the treatment phase of the study. After completion of the treatment phase, an additional two rats of each sex were exposed to one of the treated or control smokes for one exposure period for plasma nicotine determinations and compared to one untreated control rat per sex.

4. The animals were subjected to the test exposures for one 252-minute period per day (18 cigarettes), five days per week, for six weeks. Animals used for plasma nicotine determinations were exposed for one 252-minute period.

5. Food and water were withheld from all animals during exposures.

6. The chamber air flow for the exposure sequences in the 38-liter chamber followed a pattern of smoke injection, turbulence, static condition, and dynamic flow, as follows:

Smoke injection	2 sec @ 0.105 l/min	Repeated 6-8 times, until cig. smoked out	Repeated for 18 cigarettes
Turbulence	2 sec		
Static	20 sec		
Dynamic flow	36 sec @ 50 l/min		
Dynamic flow	5 min @ 50 l/min		

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Using an ADL Mark II piston-type smoking machine, room air was drawn through the cigarettes for each smoke injection. The injected smoke was dispersed into ('turbulence') and purged from ('dynamic flow') the inhalation chamber by filtered compressor air.

7. Chamber temperature and relative humidity were not assessed.

8. The test method was whole-body exposure.

9. See Item 6.

10. Particulate phase smoke samples were obtained weekly for each group. Samples were drawn onto a Gelman 25-mm thick-glass fiber in-line filter using a 100 cc Draeger bellows pump during all 20-second static periods immediately following dispersion of each cigarette puff, except the first and last in each ending session. Filters were weighed for total particulate matter, then analyzed for CGA-41065 using HPLC methods. Mean total particulate matter (TPM) averaged 29.64 to 35.91 µg/l for the control and three treated groups. Overall mean concentrations of CGA-41065 were 1.15 and 3.74 µg/l for the 5000 and 15000 ppm groups, respectively. There was no CGA-41065 detected in the control or 300 ppm group samples.

11. Aerodynamic particle size was not assessed.

12. All animals were observed twice daily for mortality and signs of pharmacological and/or toxicological effects on exposure days and once daily on the two nonexposure days between each five-day treatment sequence. All male animals appeared normal throughout the study. The few observations for female animals were not related to treatment.

13. Individual body weights were recorded immediately prior to the first exposure and at weekly intervals throughout the study. For females, there were no differences among the groups in absolute body weight at any assessment point. For males, there were no differences among the groups in absolute body weight for the first five weeks of the study. Mean body weights for all three test groups were lower than controls at Week 6, but the differences, which were less than 4%, were not considered toxicologically important.

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14. Individual food consumption was recorded weekly throughout the study. There were no differences in food consumption among the groups for either males or females.

15. Ophthalmological examinations were not performed.

16. Hematology and clinical chemistry parameters were assessed prior to the first exposure on the designated animals which were not included in the treatment phase of the study. Hematology and clinical chemistry parameters were assessed for all on-study animals immediately before terminal sacrifice. Also, plasma nicotine levels were assessed for the nine animals/sex (one control not exposed to smoke, two vehicle control, two at each dose level) which had been designated for this purpose. See Items 17 and 18 for results.

17. Hematology parameters were hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, platelet count, and reticulocyte count. There were no differences among the groups for any of the hematology parameters.

18. Clinical chemistry parameters were total protein, albumin, globulin, alkaline phosphatase, total bilirubin, calcium, potassium, urea nitrogen, glucose, aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, and total cholesterol. There were no statistically significant differences among the groups except for calcium, in which high-dose males and mid- and high-dose females had slightly lower calcium levels than their respective controls. However, the values were within the normal range and not considered to be biologically significant. Plasma nicotine levels in the test groups and vehicle control animals were at least five times greater than those of the untreated controls, indicating that the rats were inhaling significant amounts of the particulate phase of the cigarette smoke.

19. Urinalyses were not performed.

20. A gross necropsy examination was conducted on each animal at the termination of the study. Weights were obtained for brain, adrenals, lung, heart, liver, spleen, kidneys, and testes with epididymides or ovaries. Tissue portions of

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adrenals, thoracic aorta, brain (fore-, mid-, and hindbrain), esophagus, eyes, heart, large intestine, small intestine, kidneys, larynx, liver, lung with mainstem bronchi, cervical and mesenteric lymph nodes, mammary gland, nasal turbinates, optic nerve, ovaries, pancreas, sciatic nerve, pituitary, prostate, submaxillary salivary gland, thigh muscle, skin, spinal cord, spleen, sternum (bone marrow), stomach, testes with epididymides, thymus, thyroid and parathyroids, trachea, urinary bladder, uterus (corpus and cervix), and all gross lesions were fixed in 10% neutral buffered formalin. All tissues from control and high-dose animals were subsequently dehydrated in ethyl alcohol, infiltrated with and embedded in Paraplast, sectioned at 5 µm, and stained with hematoxylin and eosin. For low- and mid-dose animals, tissue portions of trachea, kidneys, heart, liver, nasal turbinates, lung with mainstem bronchi, larynx, and any gross lesions were similarly prepared.

No treatment-related gross necropsy findings were observed for any group. There were no differences among the groups for any of the various absolute organ weights or organ/body weight ratios.

21. Histopathologic examinations were performed on the preserved tissues as listed in Item 20. No treatment-related findings were observed. The most common incidental findings included mononuclear infiltrations in the trachea, heart, lung, liver, and nasal turbinates; lymphoreticular hyperplasia in the mandibular lymph nodes; and focal protrusions that are associated with a propensity for herniation of the diaphragm in Fischer 344 rats.

22. A 90-day inhalation study was not required for registration of this product. The study summarized here was designed to answer specific questions regarding the toxicity of pyrolysis products of cigarette tobacco treated with CGA-41065. Therefore, adherence to all of the Acceptance Criteria is neither expected nor appropriate. However, most of the criteria were met, especially in terms of the data collected, including body weight, food consumption, clinical observations, clinical pathology, necropsy, and histopathology. Chamber dynamics were intended to mimic cigarette smoking, and analytical data and blood nicotine levels showed that sufficient quantities of smoke were present.

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